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Brief Clinical Report

Dubowitz Syndrome in a Boy Without Developmental Delay: Further Evidence for Phenotypic Variability

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Dubowitz syndrome is an autosomal recessive condition characterized by pre- and postnatal growth retardation, eczema, telecanthus, epicanthal folds, blepharophimosis, ptosis, and broadening of the bridge and tip of the nose. The initial patients described had varying degrees of mental retardation and there is little information about long-term developmental outcome. We present a boy with Dubowitz syndrome who does not have developmental delays, providing additional evidence that the phenotype includes normal neurodevelopmental status. Am. J. Med. Genet. 68:216–218, 1997

KEY WORDS: Dubowitz syndrome; case report; normal development

INTRODUCTION

In 1965, Dubowitz described familial occurrence of low birth weight dwarfism with a unique facial appearance and eczema. Opitz et al. [1973] later recognized that these patients most likely represented a new genetic syndrome. Since then, more than 140 cases of the Dubowitz syndrome (DS) have been reported and several studies have tabulated phenotypic manifestations [Wilroy et al., 1978; Orrison et al., 1980; Küster and Majewski, 1985; Ilyina and Lurie, 1990 Tsukahara & Opitz, 1996]. The most consistent characteristics of the Dubowitz patients are pre- and postnatal growth failure, problems feeding, microcephaly, sparse blond hair, and unique facial appearance. Sloping forehead, ptosis/blepharophimosis, ear abnormalities, micrognathia, and a broad nasal bridge are the prominent facial characteristics. Mental retardation was initially thought to be a major part of the syndrome. A few patients with this syndrome were identified previously with normal development [Parrish and Wilroy, 1980; Küster and Majewski, 1985]. This patient adds evidence that some DS patients have normal development.

CLINICAL REPORT

PG is a 2 8/12 year white boy who was referred for inadequate growth and unusual facial appearance suggestive of the fetal alcohol syndrome (Fig. 1). He was adopted from Russia. His biological mother was 27 years old at time of delivery and he was the result of her second pregnancy. No history of maternal alcohol ingestion was reported. Birth weight was 2.3 kg. No other birth measurements are available. One Apgar score of 9 was recorded. Birth records mention one undescended testicle. He was described as being "sick" in the orphanage.

PG was adopted at age 9½ months. By this age, he crawled and stood alone. He began to speak at 1 year and at 26 months spoke in 2 to 3 word sentences with good articulation. He has had multiple ear infections necessitating myringotomy tube placement at 2 3/12 years. An inguinal hernia and undescended testicle were repaired at that time as well. He has had feeding difficulties since his adoption, because of mild dysphagia.

Physical Examination

At 32 months, his height was 85 cm (2.3 standard deviations below mean for age; 50th centile for 14 months), weight 10.4 kg (2.6 standard deviations below mean for age; 50th centile for 12 months; 25th centile for height age), and head circumference 47 cm (2.6 standard deviations below mean for age; 50th centile for 12 months; approximately 1 standard deviation below height age). Palpebral fissures measured 2.0 cm bilaterally (50th centile for age 4 months). Epicanthal folds were present. Outer canthal distance was 8.0 cm (near 75th centile); inner canthal distance was 3.4 cm (>97th centile) and interpupillary distance was 5.7 cm (>97th centile). Hair was blond and sparse. Nasal bridge is broad and depressed and the nasal tip was

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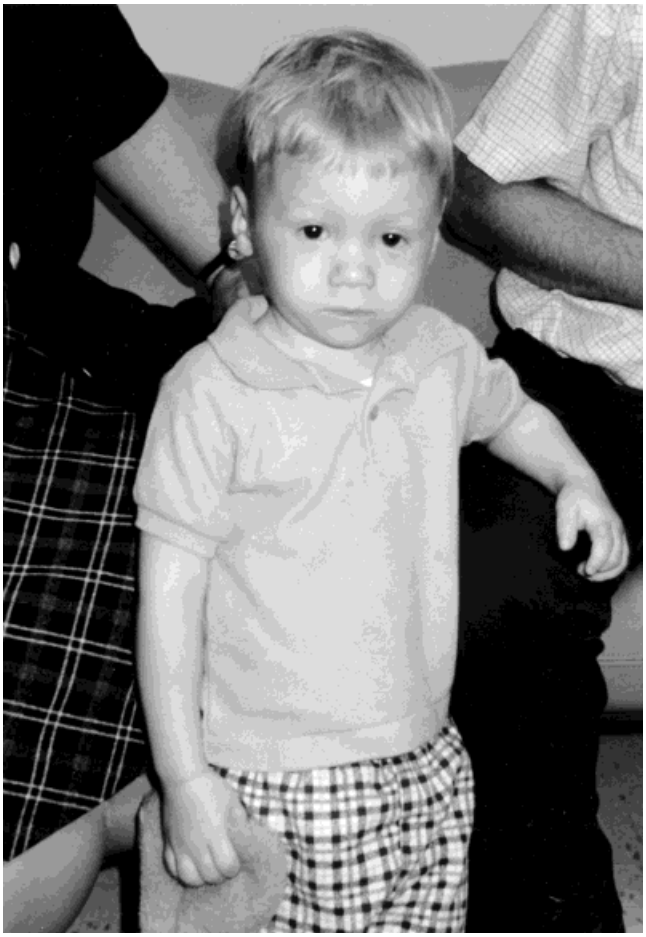

Fig. 1. Patient at 32 months. Small palpebral fissures, hypertelorism, depressed nasal bridge, thin upper lip, and proportionate small size.

broad. Upper lip was thin with a short but well-developed philtrum. He had a mild overbite with normal dentition. No body asymmetry was present. Hands showed vertical palmar creases bilaterally and unilateral clinodactyly on the right. Voice was high-pitched. There is no evidence of eczema and no birthmarks or skin abnormalities were present. Abdomen showed two well-healed surgical scars from hernia repair. Dermatoglyphic analysis of digital patterns on the left hand showed all ulnar loops. On the right hand, digits 1 through 4 showed ulnar loops and the 5th digit showed a whorl. Genitalia were normal male. Neurological examination showed no deficits.

Developmental History

Denver Developmental screening showed normal progression in development of language, self-help, social, fine motor, and gross motor skills. He was mildly hyperactive, but not unusual for age. He attends a normal day care setting. Behavior was appropriate for age, and perhaps advanced in some areas.

Laboratory Studies

Laboratory studies to date include routine blood count and chemistries, thyroid function tests, sweat testing, and chromosomes; all results were normal.

DISCUSSION

In the past, overlaps between DS and fetal alcohol syndrome (FAS) have been noted because the two conditions may share microcephaly, prenatal and postnatal growth deficiency and minor facial anomalies [Wilroy et al., 1987; Küster and Majewski, 1985; Opitz and Holt, 1990; Mathieu et al., 1991]. FAS is distinct from DS because it is associated with an increased incidence of congenital heart and spine defects, and hemangiomas, as well as the obligatory maternal history of alcohol consumption during pregnancy [Küster and Majewski, 1985; Jones et al., 1973]. Another characteristic that may eventually help to differentiate these diagnoses is intellectual function. The behavioral phenotype in patients with FAS has been consistent, while some DS patients with normal neurodevelopmental status have been identified [Janzen et al., 1995; Parrish and Wilroy, 1980].

In the present case, there was concern about FAS; however, his facial appearance, microcephaly, low birth weight, continued small stature, and feeding difficulties suggested the diagnosis of DS. Recurrent infections, inguinal hernia, and cryptorchidism, in addition to sparse blond hair and high-pitched voice, support this diagnosis. The lack of eczema is insufficient to rule out the diagnosis of Dubowitz syndrome, as only half of reported DS have eczema [Orrison et al., 1980; Gomirato et al., 1992].

Although physical characteristics of DS have now been well-documented, psychological and mental development are not so well-described. Many case reports present young children before long-term developmental outcome is known, as is true here. Long-term follow-up was reported in one patient with mild mental retardation. At age 30, she was living independently and enrolled in a sheltered work setting [Hansen et al., 1995]. No series of affected adults has yet been reported.

Approximately 80% of Dubowitz patients are microcephalic [Tsukahara and Opitz, 1996], a possible predisposition to mental retardation, yet Küster and Majewski [1985] reported normal psychomotor development in 8 of 17 Dubowitz patients. Our review of the original 20 patients (excluding those under the age of 2 years) showed that head circumference less than 2 standard deviations below height age correlated with mental deficiency [Dubowitz, 1965; Grosse et al., 1971; Opitz et al., 1973; Majewski et al., 1975; Wilroy et al., 1978]. Parrish and Wilroy [1980] reported a follow-up study of 10 patients ranging from 2 8/12 years to 9 10/12 years. All continued to exhibit an extremely small height and weight with proportionate head circumference. Results of their psychological testing documented an average intelligence in 3 patients. Seven were reported as ranging from low average intelligence to severe mental retardation. Unfortunately, only 2 of these children were of sufficient age or ability to complete a brief academic achievement test. Thus, Parrish and Wilroy [1980]

pointed out that any conclusions regarding academic performance in their series of Dubowitz patients would be premature. Our patient without developmental delay has proportionate microcephaly. The evidence suggests that disproportionately small head circumference may be a predictor of neurodevelopmental delay in DS.

A commonly reported neurodevelopmental characteristic of Dubowitz patients is hyperactivity [Wilroy et al., 1987; Parrish and Wilroy, 1980; Orrison et al., 1980; Moller and Gorlin, 1985; Mathieu et al., 1991; Tsukahara and Opitz, 1996]. Our patient displays some distractibility and a high activity level, which may be normal at 32 months. Future studies of natural history should include evaluation for this characteristic.

Most likely, Dubowitz syndrome has a range of expression with the more severely affected patients most likely to come to attention. Perhaps, as Ilyina and Lurie (1990) suggested, Dubowitz syndrome is underdiagnosed because some patients are mildly affected physically and have normal intelligence. It is also possible that a subset of patients in Byelorussia and Eastern Europe are distinct. There are no mapping studies, linkage studies or consistent biochemical markers to define a biological basis for Dubowitz syndrome, leaving open the question of genetic heterogeneity. Because such uncertainty continues, it is important to continue to report new cases of Dubowitz syndrome, especially with regard to mental and psychological characteristics. Reports of milder cases will provide a better understanding of this condition and its natural history.

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